B4 cont.

Factor IXa compound is a chemically modified form.--

--39.(Amended) The pharmaceutical composition of claim 38, wherein the chemically modified form of Factor IXa is an inactivated Factor IXa.--

B5

--42.(Amended) The pharmaceutical composition of claim 39, wherein the inactivated factor IXa compound is a Glu-Gly-Arg chloromethyl ketone-inactivated human factor IXa.--

REMARKS

Claims 23-57 were pending in the subject application. Claims 23-37, 40, 41, 43-45 and 47-57 were withdrawn pursuant to 37 C.F.R. 1.142(b). Applicants have hereinabove canceled claim 46 without prejudice or disclaimer to applicants right to pursue the subject matter of these claims in a later-filed application and amended claims 38-39 and 42. Support for these amendments may be found *inter alia* in the specification as follows: claim 38: page 17, lines 20-22; claim 39: page 10, lines 11-13; and claim 42: page 9; lines 7-10. Claims 38-39 and 42 do not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 38-39 and 42 will be pending.

Drawings:

The Examiner alleged that the drawings are objected to because in figure 5A, "CaCL" should be "$CaCl_2$." The Examiner stated that correction is required. The Examiner stated that applicant is

required to submit a proposed drawing correction in response to this Office Action. The Examiner stated that any proposal by applicant for amendment of the drawings to cure defects must consist of two parts:

(a) A separate letter to the Draftsperson in accordance with MPEP 608.02(r); and

(b) A print or pen-and-ink sketch showing changes in red ink or with the changes otherwise highlighted in accordance with MPEP 608.02(v).

The Examiner stated that the filing of new formal drawings to correct the noted defect(s) may be deferred until the application is allowed by the Examiner, but the print or pen-and-ink sketch with proposed corrections shown in red ink or with the changes otherwise highlighted is required in response to this Office Action, and *may not be deferred* [Emphasis in original]. The Examiner stated that the drawings filed April 1, 1998 were otherwise approved by the draftsman for matters of form.

In response, applicants attach hereto as **Exhibit C**, Letter with Proposed Drawing Change in accordance with MPEP §608.02(r) and as **Exhibit D**, amended figure 5A, i.e. drawing sheet 7/11, in accordance with MPEP §608.02(v). Therefore, figure 5A now recites "$CaCl_2$" and no longer recites "CaCL." Applicants contend that this letter and amendment obviate the Examiner's above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Sequence Listing:

The Examiner alleged that this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). The Examiner further alleged that this application fails to comply with the requirement of 37 C.F.R. §1.821 through §1.825 for the following reasons: The Examiner alleged that nucleotide sequences are present at pages 13-14 of the specification which are subject to the sequence disclosure rules, but no sequence listing has been submitted. Further, the Examiner alleged that SEQ ID NOS must be inserted after every sequence subject to sequence disclosure rules in compliance with 37 C.F.R. §1.821(d). The Examiner stated that the applicant must provide an original computer readable form (CRF) copy of the Sequence Listing, a substitute paper copy of the Sequence Listing as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter as required by 37 C.F.R. 1.825(a) and (b).

In response, applicants submit herewith a paper copy of a Sequence Listing as **Exhibit E** and a computer disk including a computer readable form of the Sequence Listing and a Statement of Compliance as **Exhibit F** pursuant to 37 C.F.R. §1.821-§1.825. Applicants submit that these amendments raise no issue of new matter and request that the Examiner enter these amendments.

Informalities in the Disclosure:

The Examiner stated that the disclosure is objected to because

of the following alleged informalities:

(a) The Examiner stated that at page 1, line 8, the status of the U.S. patent application should be updated.

(b) The Examiner stated that at page 6, line 21, "congenital" is misspelled.

The Examiner stated that appropriate correction is required.

In response, applicants have hereinabove amended the above-identified informalities in the specification as follows

(a) at page 1 the specification now recites:
"This application is a continuation-in-part of PCT International Application No. PCT/US97/08282, filed May 15, 1997 which is a continuation-in-part of United States Application Serial No. 08/648,561, filed May 16, 1996, **now U.S. Patent No. 5,839,443, issued November 24, 1998**, the contents of each of which are incorporated by reference in their entireties into the present application." [Emphasis added]; and

(b) on page 6, line 21 the specification now recites "congenital" rather than "congential."

Accordingly, applicants contend that these amendments obviate the Examiner's above objections and respectfully request that the Examiner reconsider and withdraw these grounds of objection.

Informalities in the Claims:

The Examiner stated that claims 39, 42 and 46 are objected to because of the following alleged informalities:

(a) The Examiner stated that at claim 39, line 4, "Ixai" should be changed to "IXai." The Examiner stated that at claim 42, line 5, "Aly" should be changed to "Gly."

(b) The Examiner stated that at claim 42, page 3 of the amendment filed February 9, 2001, line 5, "antibody" should be inserted after "monoclonal."

(c) The Examiner stated that at claim 46, line 4, "Ixai" should be changed to IXai." The Examiner stated that appropriate correction is required.

In response, applicants respectfully traverse the Examiner's above objection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 46 and amended claims 39 and 42 as follows:

(a) Applicants have hereinabove amended claim 39 such that it no longer recites "Ixai."

(b) Applicants have hereinabove amended claim 42 such that it no longer recites "Gly" or "monoclonal."

(c) Applicants have hereinabove canceled claim 46.

Accordingly, applicants contend that these amendments obviate the Examiner's above objections and respectfully request that the Examiner reconsider and withdraw these grounds of objection.

Claims 42 and 46:

The Examiner stated that claims 42 and 46 are objected to under 37 C.F.R. §1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

(a) The Examiner alleged that the factor IXa compounds recited in instant claims 42 and 46 are not species of the recombinant muteins required by claim 40, upon which claims 42 and 46 depend.

(b) The Examiner alleged that claim 42 does not further limit independent claim 38 because claim 42 recites competitive inhibitors and antibodies which are not species of the chemically modified forms and recombinant muteins required by claim 38, upon which claim 42 ultimately depends.

In response, applicants respectfully traverse the Examiner's above objection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 46 and amended claim 42 as follows:

(a) Claim 42 now recites "the pharmaceutical composition of claim 39, wherein the inactivated factor IXa compound is a Glu-Gly-Arg chloromethyl ketone-inactivated human factor IXa." Accordingly, claim 42 is in proper dependent form.

(b) Claim 42 now recites "the pharmaceutical composition of claim 39, wherein the inactivated factor IXa compound is a Glu-Gly-Arg chloromethyl ketone-inactivated human factor Ixa." Accordingly, claim 42 is in proper dependent form.

Accordingly, applicants contend that these amendments obviate the Examiner's above objections and respectfully request that the Examiner reconsider and withdraw these grounds of objection.

Rejection of Claims 38-39, 42 and 46 Under 35 U.S.C. §102(b)

The Examiner rejected claims 38-39, 42 and 46 under 35 U.S.C. §102(b) as allegedly being anticipated by Benedict et al.(J. Clin. Invest., 88:1760-1765). The Examiner alleged that the Benedict et al. article teaches an aqueous saline solution comprising bovine Factor IXa inactivated with Glu-Gly-Arg-chloromethylketone. The Examiner alleged that the composition is used as a thrombosis inhibitor at Abstract, page 1760, first full paragraph; and table 1.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claims of the present invention are patentably distinguishable from the cited reference. Applicants contend that the claims of the present invention are directed to a **pharmaceutical composition** comprising

a Glu-Gly-Arg chloromethyl ketone-inactivated **human factor IXa** compound and a **pharmaceutically acceptable carrier**, while Benedict et al. merely discloses **bovine** factor IXa. Therefore, Benedict fails to disclose any pharmaceutical composition comprising a Glu-Gly-Arg chloromethyl ketone-inactivated human factor IXa compound and a pharmaceutically acceptable carrier. Accordingly, the present invention is not anticipated by Benedict et al. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection of Claims 38-39, 42 and 46 Under 35 U.S.C. §102(a)

The Examiner rejected claims 38-39, 42 and 46 under 35 U.S.C. §102(b) as allegedly being anticipated by Wong et al. The Examiner alleged that Wong et al. teaches a bolus form of dansyl Glu-Gly-Arg chloromethyl ketone-inactivated bovine Factor IXa.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claims of the present invention are patentably distinguishable from the cited reference. Applicants contend that the claims of the present invention are directed to a **pharmaceutical composition** comprising a **Glu-Gly-Arg chloromethyl ketone-inactivated human** factor IXa compound and a **pharmaceutically acceptable carrier**, while Wong et al. merely discloses a **dansyl** Glu-Gly-Arg chloromethyl ketone-inactivated **bovine** factor IXa. Therefore, Wong et al. fails to disclose any pharmaceutical composition comprising a Glu-Gly-Arg chloromethyl ketone-inactivated human factor IXa compound and a pharmaceutically acceptable carrier. Accordingly, the present

invention is not anticipated by Wong et al. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection of Claims 38-39, 42 and 46 Under 35 U.S.C. §102(b)

The Examiner rejected claims 38-39, 42 and 46 under 35 U.S.C. §102(b) as allegedly being anticipated by Bajaj et al. The Examiner alleges that the Bajaj et al. article teaches an aqueous composition comprising human Factor IXa inactivated with dansyl Glu-Gly-Arg chloromethyl ketone. The Examiner stated that with respect to the term "pharmaceutical," an intended use limitation does not impart patentability to product claims which are otherwise anticipated by the prior art, and that the Bajaj et al. article allegedly teaches every component required to be present by applicants' claims.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claims of the present invention are patentably distinguishable from the cited reference. Applicants contend that the claims of the present invention are directed to a **pharmaceutical composition** comprising a **Glu-Gly-Arg chloromethyl ketone-inactivated human** factor IXa compound and a **pharmaceutically acceptable carrier**, while Bajaj merely discloses a **dansyl** Glu-Gly-Arg chloromethyl ketone inactivated form of factor IXa. Therefore, Bajaj et al. does not disclose the pharmaceutical composition of the presently claimed invention, i.e. a pharmaceutical composition comprising a Glu-Gly-Arg chloromethyl ketone-inactivated human factor IXa compound

and a pharmaceutically acceptable carrier. Accordingly, the present invention is not anticipated by Bajaj et al. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection of Claims 38-39, 42 and 46 Under 35 U.S.C. §102(a)

The Examiner rejected claims 38-39, 42 and 46 under 35 U.S.C. §102(a) as allegedly being anticipated by Lenting et al. The Examiner alleged that the Lenting et al. teaches an aqueous composition in which human factor IXaβ, i.e. Factor IXa, is reacted with Glu-Gly-Arg chloromethyl ketone. The Examiner stated that with respect to the term "pharmaceutical," an intended use limitation does not impart patentability to product claims which are otherwise anticipated by the prior art, and that the Lenting et al. article allegedly teaches every component required to be present by applicants' claims.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claims of the present invention are patentably distinguishable from the cited reference. Applicants contend that the claims of the present invention are directed to a **pharmaceutical composition** comprising a Glu-Gly-Arg chloromethyl ketone-inactivated **human factor IXa** compound and a **pharmaceutically acceptable carrier**, while Lenting merely disclose a **dansyl**-Glu-Gly-Arg chloromethyl ketone inactivated form of **factor IXa**β. Therefore, Bajaj et al. does not disclose the pharmaceutical composition of the presently claimed invention, i.e. a pharmaceutical composition comprising

a Glu-Gly-Arg chloromethyl ketone-inactivated human factor IXa compound and a pharmaceutically acceptable carrier. Accordingly, the present invention is not anticipated by Lenting et al.

Furthermore, applicants respectfully remind the Examiner that to anticipate a claim, the reference must teach every element of the claim. Applicants contend that Lenting et al. does teach every element of the claimed invention. Applicants respectfully point out that the claimed invention is drawn to a pharmaceutical composition comprising a Glu-Gly-Arg chloromethyl ketone-inactivated human **factor IXa** compound and a pharmaceutically acceptable carrier. In contrast, Lenting et al. merely describes factor IXaβ and recites that "FIXaβ was prepared by incubating purified FIX(4 μM) **with** human FIXa((0.23 μM)." [Emphasis added] See page 14885, first column. Further, Lenting et al. recites that "FIXaβ **and** FIXa were separated employing anion exchange chromatography." [Emphasis added] See page 14885, first column. Therefore, Lenting et al. clearly distinguishes factor IXaβ from factor IXa. Accordingly, Lenting et al. fails to teach every element of the presently claimed invention, i.e. a pharmaceutical composition comprising a Glu-Gly-Arg chloromethyl ketone-inactivated human **factor IXa** compound and a pharmaceutically acceptable carrier. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

In view of the foregoing remarks and amendments, applicants respectfully request that the above grounds of objection and

rejection be reconsidered and withdrawn and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $460.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington VA 22202.

5/6/02

John P. White Date
Reg. No. 28,678

Exhibit A

(a) Please replace the paragraph at page 13, lines 17-35 and page 14, lines 1-12, with the following paragraph:

--1) Oligonucleotides for producing Factor IXmi(Ser365→Xxx)

3'-W ACA GTT CCT CTA XXX CCC CCT GGG GTA V-5' (SEQ ID No.:1)

where

W is T, 3'-GT or 3'-AGT

V is C, 3'-CA or 3'-CAA

XXX is the complement to a DNA codon for any one of the standard amino acids other than serine.

2) Oligonucleotides for prodicing FACTOR IXmi (Asp269→Yyy)

3'-W TTC ATG TTA GTA YYY TAA CGC GAA GAC V-5' (SEQ ID No.:2)

where

W is A, 3'-TA, or 3'-TTA

V is C, 3'-CT, or 3'-CTT

YYY is the complement to a DNA codon for any one of the standard amino acids other than aspartic acid and cysteine.

3) Oligonucleotides for producing Factor IXmi (His221→Zzz)

3'-TTA CAT TGA CGA CGG ZZZ ACA CAA CTT TGA CCA-5' (SEQ ID No.:3)

where

W is A, 3'-AA, or 3'-TAA

V is C, 3'-CC, or 3'-CCA

ZZZ is the complement to a DNA codon for any one of the standard amino acids other than histidine and cysteine.--

(b) Please replace the paragraph at page 1, lines 5-10, with the following paragraph:

-- This application is a continuation-in-part of PCT International Application No. PCT/US97/08282, filed May 15, 1997 which is a continuation-in-part of United States Application Serial No. 08/648,561, filed May 16, 1996, now U.S. Patent No. 5,839,443, issued November 24, 1998, the contents of each of which are incorporated by reference in their entireties into the present application.--

(c) Please replace the paragraph at page 6, lines 15-35 and page 7, line 1, with the following paragraph:

-- This invention further provides that the patient may be subjected to extracorporeal blood circulation during transplant surgery or cardiopulmonary bypass surgery or any surgery in which obligate clamping of a blood vessel is required. The patient may be subjected to extracorporeal blood circulation during any kind of cardiac surgery, including bypass grafting, valve replacement, [congential] congenital repair heart surgery and heart transplantation. The patient may be a human being. The patient may also be subjected to extracorporeal life support. The patient may be a cardiogenic shock patient. The patient may be undergoing hemodialysis, continuous arterio-venus hemofiltration (CAVH), continuous veno-venous hemofiltration (CVVH), extracorporeal circulatory membrane oxygenation (ECMO), brain surgery, vascular surgery,

abdominal surgery, orthopaedic surgery, hip replacement surgery, transplant surgery, or any surgery requiring cardio-pulmonary bypass. The subject may be any patient requiring a mechanical circulatory assistance or ventricle assist device (i.e. LVAD). The subject may be a patient requiring new devices as described in Wickelgren, 1996 such as implantable defibrillators. The subject may also be a patient suffering with symptoms of systemic lupus erythematosus or TTP (thrombotic thrombocytopenic purpura). The subject may also be a patient requiring plasmapharesis.--

Exhibit B

--38. (Amended) A pharmaceutical composition which comprises an effective amount of a Factor IXa [or a Factor IX] compound and a pharmaceutically acceptable carrier; wherein the Factor IXa compound is a chemically modified form [or a recombinant mutein of Factor IXa [compound].--

--39. (Amended) The pharmaceutical composition of claim 38, wherein the chemically modified form of Factor IXa is an inactivated Factor IXa [, an active-site blocked Factor IXa, or a Factor IXai].--

--42. (Amended) The pharmaceutical composition of claim [40] 39, wherein the inactivated factor IXa compound is [selected from the group consisting of] a Glu-Gly-Arg chloromethyl ketone-inactivated human factor IXa [, an inactive christmas factor, a Glu-Aly-Arg chloromethyl ketone-inactivated factor IXa, aglutamyl-glycyl-arginyl-Factor IXA, a dansyl Glu-Gly-Arg chloromethyl ketone-inactivated bovine factor IXa (IXai), a Factor IXai, a competitive inhibitor of Factor IXa, a peptide mimetic of Factor IXa, a carboxylated christmas factor, a competitive inhibitor of the formation of a Factor Ixa/VIIIa/X complex, a des-y-carboxyl Factor IX, a Factor IX lacking a calcium-dependent membrane binding function, an inactive Factor IX including only amino acids 1-

47, an apoFactor IX including amino acids 1-47, a Factor IX Bm kiryu, a Val-313-to -Asp substitution in the catalytic domain of Factor IX, a Gly-311-to Glu substitution in the catalytic domain of Factor IX, a Gly-311 to Arg-318 deletion mutant of Factor IXa monoclonal, and an anti-Factor IXA polyclonal antibody].--